Rejection of Claims 54-56 Under 35 U.S.C. §112, first paragraph

Claims 54-56 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner maintains that the specification does not provide enablement for nucleotides greater than 100 or less than 8 nucleotides in length.

In view of the guidance provided in the specification one of skill in the art would have been enabled to synthesize and use nucleic acids of any size provided that they are sufficiently immunostimulatory. The specification describes the use of nucleic acids outside the range of 8-100 nucleotides in length. For instance, page 16 of the specification, lines 3-4, teaches "... nucleic acids of any size (even many kb long) are immunostimulatory if sufficient immunostimulatory motifs are present...". Over 300 oligonucleotides of different sizes and/or base content were evaluated for their immunostimulatory effects (description in specification beginning on page 21). Procedures for synthesizing oligonucleotides of different sizes are known in the art. Additionally, the specification described methods to determine the immunostimulatory effects of these nucleic acids. Although the oligonucleotides shorter than 8 bases in the specific examples tested were found to be nonstimulatory, sequences as short as 6 bases have been found to be stimulatory. The specification provides adequate support for one of ordinary skill in the art to synthesize and administer oligonucleotides shorter than 8 bases in length. Thus, the specification provides sufficient enablement for the nucleic acids as described in the present claims.

Rejection of Claims 42-58 Under 35 U.S.C. §112, first paragraph

Claims 42-58 are rejected under 35 U.S.C. §112, first paragraph "...as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art...to make and/or use the invention." The Examiner has found that the Applicant's arguments, the Declaration of Dr. Krieg (submitted July 25, 2001) and the seven exhibits attached to said declaration are not persuasive because the arguments, declaration and exhibits do not make a connection between the administration of the CpG oligonucleotides and the induction of a Th1 from a Th2 immune response. The Applicant respectfully disagrees.

The Applicant has provided two working examples of CpG oligonucleotides administered *in vivo* that showed directly the induction of a Th1 immune response. The details (which include the mode of administration, the dosage and the time and frequency of administration) of one experiment was provided in the specification and the other in Exhibit 7. Example 12 of the specification described the immune response in a murine model of asthma subsequent to the *in vivo* administration of CpG oligonucleotides. The details, provided on pages 64-65, describe the intraperitoneal injection of 30μg CpG oligonucleotide per 200μl saline in 6-8 week old mice immunized at day 0 and 7. Subsequent to this administration the resulting data showed an increase in IL-12 production (indicative of a Th1 response) contrary to the inflammatory response in the absence of CpG administration where a cytokine indicative of a Th2 immune response (IL-4) was produced. The results showed the direct shift to a Th1 from a Th2 immune response as evidenced by the IL-12 versus IL-4 cytokine production.

Exhibit 7, previously provided with the response mailed on July 23, 2001, also showed a shift to a Th1 immune response as a result of CpG oligonucleotide administration in an *in vivo* system. This was evidenced by greater IgG2a levels relative to IgG1 levels in mice. In this example mice were immunized by intranasal inhalation with HBsAg alone or in combination with CT and/or CpG containing ODNs. The mice were administered 1μg of the CpG ODNs at 0 and 8 weeks. The isotypes measured at 8 weeks post prime and 4 weeks post boost showed that the IgG2a/IgG1 ratio indicated a Th1-like response when the mice were administered the CpG ODNs with and without CT. This example supports, as asserted by and shown in a working example by Applicant in the specification, that CpG induces a shift from Th2 to a Th1 immune response.

Additionally, there are many examples in the specification of a connection between CpG oligonucleotide administration and a shifting of the immune response from Th2 to Th1. The specification demonstrates that nucleic acids containing unmethylated CpG dinucleotides redirect a subject's immune response from Th2 to Th1 by inducing monocytic cells as well as other cells to produce the cytokines which are indicative of Th1. These cytokines include IL-12, IFN-γ and GM-CSF. Additionally, the specification also provides a description of acceptable forms of administration (page 54, lines 6-20), times and frequencies of administration (page 53, lines 5-11 and 19-25), as well as effective amounts (page 54, line 21 to page 55, line 1).

Based on the working examples and the description provided in the specification, as well as the level of skill in the art, one of skill in the art is sufficiently enabled to practice the claimed invention. The practice of the invention as described in claims 42-58 would not require undue experimentation.

Rejection of Claim 42 Under 37 CFR 1.75

Claim 42 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 44. Applicant has cancelled claim 44.

Summary

In view of the foregoing, the Applicant respectfully requests the Examiner reconsider and withdraw the rejections. This application should now be in condition for allowance. A notice to the effect is respectfully requested. If the Examiner believes that after considering these remarks the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the number listed below.

Respectfully Submitted,

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